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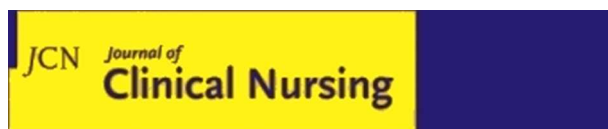
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Predictive or not predictive: understanding the mixed messages from the patient's DNA sequence

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Predictive or not predictive: understanding the mixed messages from the patient’s DNA sequence

For Peer Review

Abstract***Aims and objectives***

The aim of this discussion paper is to enable nurses to understand how deoxyribonucleic acid analysis can be predictive for some diseases and not predictive for others. This will facilitate nurses to interpret genomic test results and explain them to patients.

Background

Advances in technology mean that genetic testing is now commonly performed by sequencing the majority of an individual's genome or exome. This results in a huge amount of data, some of which can be used to predict or diagnose disease.

Design

This is a discussion paper.

Methods

This paper emerged from multiple discussions between the three authors over many months, culminating in a writing workshop to prepare this text.

Results

The results of DNA analysis can be used to diagnose or predict rare diseases that are caused by a mutation in a single gene. However, while there are a number of genetic factors that contribute to common diseases, the ability to predict whether an individual will develop that condition is limited by the overall heritability of the condition. Environmental factors (such as lifestyle) are likely to be more useful in predicting common disease than genomic testing. Genomic tests may be of use to inform management of diseases in specific situations.

Conclusions

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Genomic testing will be of use in diagnosing disorders due to single gene mutations, but the use of genomic testing to predict the chance of a patient being affected in the future by a common disease is unlikely to be a realistic option within a health service setting.

Relevance to clinical practice

Nurses will increasingly be involved in the use of genomic tests in mainstream patient care. However, they need to understand and be able to explain to patients the practical applications of and limitations of such tests.

Summary box

What does this paper contribute to the wider global clinical community?

- Genomic testing enables a person’s genome to be studied
- Genomic testing is useful in diagnosis or prediction of rare genetic disorders
- Due to the low heritability of many conditions, it is unlikely that results of genomic tests will be of practical utility in predicting common disease.

Key words

Nursing, genomic, genetic, predictive power, heritability, gene association, genetic susceptibility, pharmacogenomics.

Introduction

Aims

Genetics and genomics (see Box 1) are increasingly part of mainstream healthcare.

The aim of this discussion paper is to enable nurses to understand how DNA analysis (used in both genetic and genomic contexts) can be predictive for some diseases and not predictive for others. This will facilitate nurses to interpret DNA results and explain them to patients.

Background

Historically, genetic testing has been offered to patients affected by or at risk of a rare genetic condition that is known to be caused by a variation in a single gene.

Targeted tests have enabled analysis of a specific sequence of deoxyribonucleic acid (DNA) in a gene or genes associated with the condition. Due to advances in technology, it is now becoming more efficient to perform a test which results in a sequence of the majority of the individuals' DNA or the coding sequences (exons) within the DNA (Korf 2013).

Genome sequencing (for definition, see Box 2) is envisioned to ultimately replace conventional forms of genetic testing (Manolio *et al.* 2013, Wright *et al.* 2013). The technology will become so inexpensive that it will be straightforward to sequence the entire genome and only interpret the loci of interest. This prospect has already led to an intense debate on what to do with the remaining unreported data (Burke *et al.* 2013, Green *et al.* 2013). The return of unexpected, or 'incidental', findings is one of many concerns accompanying the introduction of genome sequencing in health care. Others include issues around privacy, discrimination, insurability, and patient and

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consumer protection (Hens *et al.* 2013, Jackson *et al.* 2012), all of which have relevance to holistic nursing care.

The announcement of the projects such as the 100,000 genome project in England (Genomics England 2014), a transformative programme for the National Health Service is an additional impetus for the whole health service workforce to engage with genomics. As whole genome and whole exome sequencing (Box 2) is introduced into health care the landscape of genetic testing will drastically change (Manolio *et al.* 2013) because the information that is obtained from sequencing is much more complex than the results of traditional genetic testing. Where traditionally a test was undertaken to inform a single health outcome, genome sequencing can inform the diagnosis of, or susceptibility to, numerous diseases (Ashley *et al.* 2010). Increasingly nurses are involved in offering genetic testing and may therefore be asked to explain tests based on sequencing, to obtain informed consent and to explain results. It is therefore important that they understand the power of such tests to predict specific conditions in the patient.

It is claimed that there are opportunities for the results of genomic tests to detect and inform management of disease (Downing *et al.* 2011), however this depends in large part on the predictive ability of a test. The predictive ability determines whether the test is able to distinguish a group of people who have a higher risk of disease than others. How much higher their risk needs to be, depends on the potential harms and benefits of correct and incorrect medical decisions that follow the test results. Therefore, the discussion of these concerns in the context of sequencing should start from a critical assessment of the predictive ability of DNA, which is paramount

because the genome does not have an 'overall' predictive ability as such. Rather, genome sequencing should be seen as one assay that consists of numerous tests (Zimmern & Kroese 2007). The predictive ability depends on what is predicted, in whom and how (using which specific information from the DNA).

For a constructive debate on clinical and ethical issues, health care professionals need to be aware of the possibilities and limitations of sequencing. A good understanding of what can (and cannot) be predicted from our DNA is necessary to ensure a responsible introduction of genome sequencing in health care and an effective regulation of commercial DNA testing.

Design

This is a discussion paper. The focus of the paper was developed as a result of the authors' involvement in an expert group on genetic testing, where it became apparent through discussions that there was a lack of understanding in health professionals of the predictive power of genetic tests.

Method

The authors formed a small nominal group to develop the paper. All of the authors have long-standing expertise in genomic healthcare and two are nurses. Initially, discussions on the content focussed on the breadth of genetic tests and the use of those tests. A draft paper was written: a face to face meeting was then convened to enable the authors to discuss in depth the relevance of the material to nurses in practice. The final paper was the result of consensus between all three authors.

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Results

What determines predictive ability?

The predictive ability of a test is determined by the incidence of disease, the frequency of the mutation (or polymorphism) and the association between the mutation and the disease. These three parameters uniquely specify the contingency table from which all test performance measures can be calculated (Box 3). For prediction, the association is of key importance: the stronger the association, the higher the risk difference between carriers and non-carriers of the mutation. Yet, strong association alone is not enough.

The incidence drives the absolute risk for carriers and non-carriers: the positive and negative predictive value. If the disease is common, the risks in those who carry the gene variation can be markedly increased even when the association is not strong, but if the disease is rare, even very strong association will yield relatively low absolute risks in carriers. A 2-fold increase of an average (prior) risk of 30%, increases the risk to maximally 60%, but a 10-fold increase of a prior risk of 0.1%, increases the risk for carriers maximally to 1%—much higher than the prior risk, but still low.

Finally, the frequency of the mutation drives the sensitivity and specificity of the test. When a disease is common but the mutation is rare, the sensitivity remains low even when the association is very strong, simply because most patients will not carry the mutation. Carrying a strongly-associated rare mutation will substantially increase the risk of disease, but only in a small minority of patients.

What can a DNA sequence reveal?

The predictive ability of DNA depends on the degree to which genes contribute to the development of disease (or other health outcome of interest), the heritability (Janssens *et al.* 2006). We discuss the three most common types of outcomes that are predicted from DNA and which vary in genetic origin and degree of heritability: monogenic disorders, treatment outcomes and susceptibility to common diseases.

Monogenic disorders

Inherited single gene disorders are conditions caused by changes to specific single genes, with no or very little impact from environmental factors. There is robust evidence for many genes associated with specific conditions, investigated in families, and there is emerging scientific consensus over methods of assigning causative genes to diseases and determining the pathogenicity of mutations in monogenic disorders (Kenna *et al.* 2013).

The predictive ability of genetic testing for monogenic disorders, or monogenic subsets of multifactorial diseases, is very high when the mutations are known. Genetic testing can be used to diagnose the disease, in symptomatic and asymptomatic phases of the disease; to test family members of patients who wish to know about their future disease; to test prenatally and enable choices about the management of the pregnancy; and, before pregnancy, to identify couples at high risk of having a child affected by an autosomal recessive condition.

Mutation testing for monogenic diseases is very predictive, but its usefulness depends on the purpose of testing and on the populations and mutations that are tested. For example, DNA testing for autosomal dominant mutations that cause mature onset diabetes of the young (MODY) (Shepherd *et al.* 2001) might be useful for relatives of MODY patients, but is unlikely to benefit the prevention of diabetes in

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the general population; the sensitivity of MODY testing is too low because most people will develop diabetes through other causes. The interpretation of genetic tests results also warrant caution when not all mutations are known or tested. In these situations, the presence of mutations is very informative (high positive predictive value), but the absence is not (low negative predictive value) because individuals who do not have the tested mutations may still carry others.

Treatment outcomes

Pharmacogenomics targets variations in the genome that are related to treatment response, dosing and adverse side effects. Several genes, such as those in the cytochrome (CYP) and human leukocyte antigen (HLA) gene groups (Sim *et al.* 2013, Wei *et al.* 2012), are associated with responses to a wide range of medications. Some associations are extremely strong and make genetic testing an evident first step in decisions about treatment, whereas others are much weaker yet statistically significant. An example of the first is *HLA-B*5701* and hypersensitivity reactions to abacavir, a treatment that reduces the amount of virus in the blood of HIV patients (Thompson *et al.*2012). An example of the second is *CYP2C19* and clopidogrel, which reduces the risk of adverse cardiovascular events after coronary stenting (Holmes *et al.*2011), but maybe not enough to justify pharmacogenetic testing. The scientific basis of most pharmacogenomic associations is far less robust than tests for monogenic disorders, although in some specific examples (as above) the clinical use of these associations will be valuable.

Susceptibility to common diseases

Most common diseases, such as cardiovascular disease, type 2 diabetes and asthma, are caused by a complex interplay of many genetic and environmental risk factors. Single risk factors, whether genetic or non-genetic, typically have only a minor impact on disease risk.

Genetic prediction of common disease is done using risk models in which the effects of multiple genetic variants are considered simultaneously. The assessment of the predictive ability follows the same principles as presented in Box 3, albeit more complex. There is not one odds ratio and frequency to consider, but many, and there is not one combination of sensitivity and specificity, but a range that is known as the receiver operating characteristic (ROC) curve (Hanley & McNeil 1982). Similarly, there is not one positive predictive value and negative predictive value, but again a range, the risk distribution.

For most diseases the predictive ability of genetic testing is limited and far lower than risk models that are based on non-genetic risk factors such as diet, exercise, alcohol consumption and smoking (Bao *et al.* 2013). However, there are exceptions. For example, the predictive ability of genetic testing for age-related macular degeneration and coeliac disease is substantially higher because the risk models include one or more variants that are strongly associated with disease risk (Romanos *et al.* 2013, Seddon *et al.* 2013).

While the predictive ability is expected to increase with more discoveries of susceptibility variants, it may not become high. Since the maximum predictive ability is limited by the heritability (Table 1), genome sequencing will predict diseases with varying degrees of accuracy even if the genetic origins of diseases are completely understood. This moderate predictive ability implies that the genetic prediction of common diseases will likely have limited utility for health care. It was argued that

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DNA testing could be used to motivate people to adopt a healthier lifestyle, but multiple studies have not shown such motivational effects (Bize *et al.* 2012). Whether the predictive ability is high enough to stratify screening programs, such as mammography screening for breast cancer, remains to be investigated (Chowdhury *et al.* 2013).

Conclusions

Achieving understanding of the concept and determinants of predictive ability will put into perspective some of the main concerns expressed in relation to DNA sequencing. First, the use of genomic testing to predict the chance of a patient being affected in the future by a common disease is unlikely to be a realistic option within a health service setting. This is because many different genetic variants, as well as environmental influences, contribute to development of common diseases. Second, for the same reason as above, although there may be unexpected findings as a result of genomic testing, these are unlikely to be of relevance to patient care unless they relate to mutations in genes known to cause single gene disorders. Third, genetic discrimination and stigmatisation on the basis of multifactorial traits is not realistic, as the predictive value of DNA testing is too low. It is unlikely that insurance companies can use genetic information to differentiate those at high or low risk of common diseases with any degree of practicality.

In terms of nursing education and practice, it is clear that nurses have a role in informing and guiding patients who are considering genetic testing. It can be argued that it is not ethical to raise expectations of the utility of genetic test results inappropriately but, in order to help patients set reasonable expectations, nurses must be informed themselves about these issues. In addition, nurses have a duty to

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help ensure that scarce health resources are used wisely and, whether testing is funded by the state, insurance company or the patient, expenditure that will not substantively contribute to patient health and wellbeing should be avoided.

While it is important that genetics and genomics are taught within in nursing curricula, equally important are the applications of these sciences to healthcare. As these topics are relevant to virtually every aspect of health and disease, we would suggest that encouraging discussion of how genetics and genomics apply in health promotion, disease prevention and disease management across the range of systems will encourage nurses to think about the issues more readily when in practice. A wide range of possible examples can also be used as the focus for discussion of ethical and professional practice, as well as stimulating nurses to think about the evidence base for care, for example the use of pharmacogenomic testing.

Ethical and societal discussions of the introduction of genome sequencing should be based on what can and cannot be predicted. Use of DNA testing can be very informative for diagnosing monogenic disorders and syndromes and for non-genetic purposes as ancestry, paternity and forensic testing, but it is not so predictive for most common diseases and traits. A patient's DNA may tell us more about the past and present than about the future.

Relevance to clinical practice

When explaining genomic tests and/or results to patients, it is important to differentiate between test results that can offer predictive information for the patient, and those with less relevance to their healthcare. Patients should be aware that unexpected findings could result from the use of genomic approaches to testing their

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DNA. Use of genomic testing to identify gene variants that could predispose the patient to common diseases are unlikely to of consequence in the context of insurance. However, genomic testing may help to inform choice of therapy in the management of some specific conditions.

For Peer Review

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Box 1. Definitions of genetics and genomics according to the World Health Organisation (2015)

Genetics is the study of heredity

Genomics is defined as the study of genes and their functions, and related techniques.

The **main difference** between genomics and genetics is that genetics scrutinises the functioning and composition of the single gene whereas genomics addresses all genes and their inter relationships in order to identify their combined influence on the growth and development of the organism. (World Health Organisation,2015)

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Box 2. Definitions of genome and sequence

Genome

Complete genetic information encoded by a persons DNA

Genome sequence

The order of the bases or DNA nucleotides in the genome. Other relevant terms are:

Targeted sequence -sequencing a specific portion of the DNA eg specific genes such as BRCA1 and BRCA2

Exome sequence- sequencing the exons of genes-the portions of the gene that codes for proteins

Whole genome sequence- sequencing the total genome.

Box 1 Calculation of predictive ability

		Disease		
		Yes	No	Total
Mutation	Present	<i>a</i>	<i>b</i>	<i>a+b</i>
	Absent	<i>c</i>	<i>d</i>	<i>c+d</i>
	Total	<i>a+c</i>	<i>b+d</i>	<i>n</i>

This table can be uniquely constructed from three parameters:

- Disease risk, e.g., the 10-year incidence: $(a+c)/n$
- Frequency of mutation: $(a+b)/n$
- Strength of association between mutation and disease risk:

Odds Ratio (OR): ad/bc , or

Relative Risk (RR): $(a/(a+b))/(c/(c+d))$

From the table, all test performance characteristics can be calculated:

- Sensitivity (Se): $a/(a+c)$
- Specificity (Sp): $d/(b+d)$
- Positive Predictive Value (PPV): $a/(a+b)$
- Negative Predictive Value (NPV): $d/(c+d)$
- Likelihood Ratio of positive result (LR+): $(a/b) / ((a+c)/(b+d)) = \text{Se} / (1-\text{Sp})$
- Likelihood Ratio of negative result (LR-): $(c/d) / ((a+c)/(b+d)) = (1-\text{Se}) / \text{Sp}$
- Risk Difference: $(a/(a+b)) - (c/(c+d))$

Table 1. Heritability estimates of various complex diseases and traits

Disease or trait	Heritability
Eye color	>99%
Type 1 diabetes	88%
Schizophrenia	81%
Alzheimer's disease	79%
Height	70-87% (m), 68-85% (w)
Obesity	65-84% (m), 64-79% (w)
Smoking persistence	59% (m), 46% (w)
Anorexia nervosa	56%
Rheumatoid arthritis	53-65%
Panic disorder	43%
Prostate cancer	42%
Migraine	40-50%
Heart attack	38% (m), 57% (w)
Smoking initiation	37% (m), 55% (w)
Depression	37%
Colorectal cancer	35%
Anxiety disorder	32%
Homosexuality	30% (m), 50-60% (w)
Breast cancer	27%
Type 2 diabetes	26%
Lung cancer	26%
Happiness	22% (m), 41% (w)

Table 1 is adapted from (Janssens & van Duijn). Heritability and frequency estimates are obtained from published studies and meta-analyses. References for the heritability estimates are provided in the original table. m=men, w=women.